Early Diagnosis of Malignant Melanoma of the Skin

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• About five per cent of all malignant lesions of the skin are malignant melanomas. The poor prognosis associated with this malignant lesion emphasizes the importance of early diagnosis. A large proportion of malignant melanomas arise in preexisting lesions such as junction nevi, precancerous melanoses and, much more rarely, blue nevi. Early malignant changes in these precursor lesions include increasing pigmentation, enlargement, thickening, crusting, bleeding, ulceration, tumor formation, and development of satellite lesions.

Many pigmented, and some non-pigmented, lesions of the skin must be differentiated from malignant melanoma. Since even with radical surgical treatment the prognosis of malignant melanoma is poor, junction nevi which are subject to continual trauma or have signs of probable malignant degeneration should be prophylactically excised.

PRIMARY MALIGNANT MELANOMA occurs most frequently in the skin and adjoining mucous membranes, next most frequently in the eye and least frequently in the meninges. Primary occurrence elsewhere is very doubtful, and in any case is conceded to be extremely rare. Malignant melanoma constitutes approximately 5 per cent of all malignant lesions of the skin.[6] In the skin of the lower extremities, however, more than 50 per cent of all malignant tumors are melanomas.[3, 9] Because of this relative frequency and the high degree of malignancy and poor prognosis, malignant melanoma is a continuing challenge.

The authors recently studied 454 cases of clinically diagnosed malignant melanoma to determine which clinical and histopathological factors might be used in an earlier and more certain diagnosis. This presentation summarizes the clinical factors which appeared, in study of these cases and of the extensive literature, to be of value in diagnosis. The statistical and histopathological findings from the study will be reported elsewhere.[2]

Most observers agree that the melanoblast, from which the malignant melanoma develops, is found only in the skin, the mucocutaneous junctions, the conjunctiva, iris, retina and choroid of the eye and the leptomeninges. It is now quite certain that most, if not all, malignant melanomas develop from preexisting lesions. At least as far back as 1857 pigmented nevi were definitely pointed out as precursors of malignant melanomas.[10]

Suggestions were made from time to time as to which type of mole, nevus or birthmark was most likely to become malignant, but these suggestions were nearly always wrong. Not until quite recently has it become clear which type of nevus most frequently gives rise to malignant melanoma.

PRECURSOR LESIONS

The precursor lesions of malignant melanomas of the skin are, in order of importance, the junction nevus, the precancerous melanosis and lentigo maligna, the junction compound nevus and the blue nevus. It is evident that the recognition and proper evaluation of these antecedent lesions are of paramount importance in arriving at an early diagnosis and prompt start of prophylactic treatment of malignant melanoma.

The junction nevus, so called because nevus cells are found at the junction of the dermis and epidermis, was named by Sattenstein, the name being later popularized and clinically interpreted by Traub and Keil.[12] The most common pigmented nevus, at least in the first three decades of life, is a light brown to jet black macular lesion, sometimes slightly elevated in the center. The surface is nearly always smooth, occasionally granular, and is free of coarse hair. The size varies from less than 1 mm. to more than 1 cm., but nearly all junction nevi are between 2 and 5 mm. in size. They may be found anywhere on the skin, including the mucocutaneous areas, and occur in all races. The average number found in a patient is said to be about twenty. The authors conclude from their studies that this estimate is probably too low, having actually counted as many as 640 clinically typical junction nevi in one adult patient.

Lentigo appears to be an early form of junction nevus, always smooth and macular, often occurring in great numbers, and microscopically identical with the junction nevus except that the nevus cells do not tend to occur in clusters or theques and are all intra-

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epidermal. Lentigo apparently has less tendency to become malignant than has the typical junction nevus.

Precancerous melanosis is much rarer than the junction nevus but is much more likely to become malignant. Precancerous melanosis develops in older persons, usually on the face, as a light to dark brown spot which slowly enlarges peripherally until, for instance, it may cover a large part of the cheek. Satellite spots may appear and may become confluent with the first lesion. Malignant change usually does not occur until the melanosis has been present for several years; such change, commonly found at the periphery, is indicated by palpable infiltration and the presence of nodules. The term "lentigo maligna," which is used by some writers as a synonym for precancerous melanosis, has been applied in the past to several different conditions. The authors apply it to a melanoma originating in a lentigo, forming a superficial, intra-epidermal malignant melanoma, usually of slow growth and late metastasis.

The junction compound nevus is microscopically a combination of a junction nevus and a dermal nevus. It is an elevated, firm lesion (rarely soft), usually nodular, rounded or dome-shaped, with a smooth or slightly verrucous surface, often containing dark coarse hairs. A junction compound nevus always has areas of pigmentation. The dermal nevus has nevus cells only in the dermis, while the compound junction nevus has nevus cells also in the epidermis or at the epidermal-dermal junction. The development of a malignant melanoma from a compound junction nevus, is much rarer than from a junction nevus, and probably occurs only when such a lesion is subject to repeated trauma. No cases are known in which it was clearly established that a malignant melanoma arose from a non-pigmented, nodular, purely dermal nevus.

The blue nevus contains spindle-shaped melanoblasts (which are believed to be of mesodermal origin in this lesion), located in the dermis in small or large groups. It is a pale blue to dark blue macular to nodular lesion, usually deep-seated, most commonly seen on the hands, feet, face or buttocks. It is usually slightly larger than a junction nevus of average size. Although a blue nevus rarely becomes malignant, the authors have recently observed a patient in whom a blue nevus of the sole of the foot became malignant and metastasized to the regional inguinal lymph nodes.[1]

EARLY MALIGNANT CHANGES

The earliest signs of the development of a malignant melanoma are usually the changes seen in a junction nevus when it undergoes malignant degeneration. These changes do not always occur in the same order, but most frequently there is first noted a darkening of color in the nevus, then an increase in size or a thickening or elevation of the lesion. Further changes may include crusting, ulceration, bleeding, or the development of a nodular tumor. In other cases there is a spilling of pigment into the adjacent skin, or small satellite lesions may appear close to the original nevus. Still later more distant metastases in the skin or regional lymph nodes may develop, or distant visceral metastases may be noted first. Clinical evidence of malignancy in some junction nevi which have already changed into melanomas is so scant—perhaps only a slight increase in pigmentation and barely palpable infiltration—that they are overlooked when search is made for a primary lesion after metastases have become clinically evident.

In a few cases of malignant melanoma of the skin no precursor lesion is clinically evident. The authors have observed at least two such occurrences in patients who had been under observation for other skin conditions, and in whom amelanotic melanomas developed on the face without grossly visible antecedent lesions. In such instances small groups of nevus cells may be present in the epidermis which are not detectable to the naked eye. These may give rise to a malignant melanoma as readily as a larger aggregate of the same cells. The authors have recently seen a section from a primary melanoma of the foot which was less than 2 mm. in diameter and light brown in color but had already given rise to regional lymph node metastases. The malignant change microscopically evident in the antecedent junction nevus was limited to a single rete peg.

In those cases in which no precursor lesions have been noticed, the malignant melanoma may first appear as a pigmented macular lesion which becomes infiltrated, or as a pigmented or non-pigmented nodule or tumor.

After a precursor lesion begins to undergo malignant degeneration, the various changes indicative of malignancy may follow each other in rapid succession, so that within a period of less than two months a fully developed melanotic tumor with metastases may be present. In other cases, particularly those arising in precancerous melanosis or in lentigo, successive changes may be very slow, and metastases from such a melanoma may not occur for years.

How soon metastases may occur after visible changes first appear in a precursor lesion is illustrated by the case of a patient who had had a flat pigmented nevus on the left side of the abdomen all his life. Three weeks before the authors' examination there seemed to be some increase in pigmentation

and a slight enlargement of the nevus. The lesion was widely excised for biopsy, and then radical excision of a large part of the skin of the abdomen was done by a competent general surgeon. No lymph nodes were palpable at that time, and because of uncertainty as to where regional metastasis might have occurred, no groin or axillary dissections were done. There was no local recurrence of the disease but metastases developed almost simultaneously in the contralateral axillary lymph nodes and in the liver, and the patient died of general metastases within two years of the time he first noticed changes in the junction nevus, despite the fact that adequate excision of the primary tumor was done only three weeks after the initial changes became apparent.

Malignant melanoma may spread in several ways. There may be local extension of the disease, sometimes to a pronounced degree. There may be metastases by way of the lymphatic system to adjacent skin areas and to the regional lymph nodes, from which the dissemination may continue through the lymphatic system or through the bloodstream. Metastases may also occur directly from the primary lesion via the bloodstream, causing early widespread metastases. Probably no other tumor tends to metastasize as early and as widely as malignant melanoma: in some cases almost every organ and type of tissue in the body is involved. The earliest symptoms of malignant melanoma may be those arising from the internal metastases, such as to the brain, lung or pancreas, the primary lesion having been unnoticed. On the other hand, after a primary malignant melanoma has been removed the metastatic lesions may not be clinically evident for decades.[5] A primary melanoma may be without visible pigment (a so-called amelanotic melanoma), and metastases from a pigmented malignant melanoma may also be without pigmentation, although microscopically some areas of melanin deposit can be seen in most of these amelanotic lesions.

Although malignant melanoma may arise at any age, the incidence steadily increases with advancing years, and the prognosis is far better before puberty than in later life because there is less tendency to metastasize.[11] apparently owing to endocrine factors which have not yet been specifically determined. These endocrine factors seem to have an opposite effect in pregnancy, where increased pigmentation of nevi is commonly noted, and where there seems to be an increased susceptibility toward malignant degeneration of junction nevi, with early rapid spread of metastases and unusually poor prognosis.

There is no significant difference in the incidence of malignant melanomas in males and females. No race seems to be exempt from this tumor, although there is a higher incidence of melanoma in the light-skinned races. The incidence in Negroes is about one-third that in Caucasians.[4, 7] Most melanomas occur from the fifth to the eighth decade of life, the peak being reached near the age of sixty. The most common site of malignant melanoma is the lower extremities, next the head and neck, and next the upper extremities. The number found on the feet far exceed the number found on any other comparable area. Melanomas are often diagnosed late in the anorectal area, the vulva and vagina, the mouth, and the mucous membrane of the nose.

Melanin may be found in the urine of patients with malignant melanomas if the elaboration of melanin is high. Sometimes this is of prognostic value. If the primary tumor has been adequately excised and no metastases can be demonstrated, and yet there is a definite steady elimination of melanin via the kidneys, visceral metastasis has occurred. Occasionally melanin production is so marked that general pigmentation or melanosis of the skin and mucous membranes takes place. Melanin phagocytized by the regional lymph nodes from a malignant melanoma has at times led to a mistaken diagnosis of metastatic melanoma when actually no malignant cells were present.

DIFFERENTIAL DIAGNOSIS

There are certain lesions of the skin with which malignant melanoma is commonly confused. It is beyond the scope of this presentation to list all such lesions, but a few are common and important. Probably all forms of pigmented lesion should be considered in the differential diagnosis of malignant melanoma. The most common and important of these is, as previously explained, the flat pigmented junction nevus. At times it is clinically impossible to be absolutely certain of the benign or malignant character of a particular lesion. In such cases surgical removal and microscopic study are necessary, and by this means it is possible to determine, in practically every instance, whether a lesion of this type is still a nevus or has changed to a malignant melanoma.

Other pigmented lesions which are confused with malignant melanoma are compound junction nevi, blue nevi, seborrheic and senile keratoses, pigmented basal cell epitheliomas, pigmented or hemorrhagic sarcomas, subepidermal fibromas, hemangiomas, hematomas, accidental tattoo marks, plantar warts and fixed drug eruptions. Nearly all of these can be quite easily differentiated clinically if the lesion is examined thoroughly, although biopsy may be necessary to diagnosis of pigmented basal cell epithelioma, blue nevus, hemangioma, and hematoma, particularly if the last-named is subungual.

Of the non-pigmented lesions which need to be differentiated the pyogenic granuloma is the most important. It usually has a pink to light red color, and a dark crust from previous hemorrhage may increase the resemblance to melanoma. The lips, the nail folds, and the feet are the sites of predilection for this lesion, but it may appear anywhere, particularly on the face. Usually it appears after trauma or infection, grows rapidly (in days instead of weeks as compared with the melanoma), and bleeds upon slight trauma. Although clinically this lesion can usually be differentiated quite readily, in many cases microscopic examination is necessary to make the diagnosis final.

A non-pigmented malignant tumor, particularly if it is fungating, may be confused with amelanotic melanoma. Papillary or fungating squamous cell carcinoma, especially if it appears on the feet, may be difficult to differentiate clinically. Many non-pigmented melanomas have been mistaken for squamous cell carcinoma, even microscopically, until the metastases clearly revealed the true nature of the tumor.

PREVENTIVE TREATMENT

Authors who have studied large series of patients treated for malignant melanoma differ greatly in their report of the mortality rates and life expectancy in these patients. Pack, Perzig and Scharnagel[8] reported an over-all five-year salvage rate of 9.7 per cent and a 17.7 per cent five-year salvage rate in surgical removal of localized melanomas. In selected cases with very radical surgery such as hemipelvectomy and thoracoscapular amputation, a higher salvage rate can probably be attained. It seems clear, however, that even with the best of treatment and under the most favorable circumstances the prognosis of malignant melanoma in adults is poor. Prophylactic treatment, therefore, becomes important. Since most malignant melanomas develop from junction nevi, the intelligent management of these is an essential part of such preventive treatment.

In the cases observed by the authors, as in all other reported series in which the history of trauma was given consideration, irritation and injury have been suspected to be a frequent initiating cause of malignant degeneration in pigmented nevi. Avoidance of trauma to pigmented nevi, particularly of the junction variety, becomes the first consideration in the preventive treatment of malignant melanoma. Patients should be instructed that picking and scratching pigmented moles is dangerous. Junction nevi which are situated where they must unavoidably be subject to friction or other chronic irritation should be excised. Such locations of chronic traumatization are the feet, the waistline, the brassiere area, the fingers and palms, and the neck and beard area in men. Perhaps the shoulders and scapular area should also be included. Junction nevi on the genitalia should also be excised prophylactically. Any junction nevus which has any of the signs of malignant degeneration previously mentioned should be excised with a good margin for microscopic study. Although it is certainly possible to destroy a junction nevus by various methods, including electrocoagulation, all methods except adequate surgical excision should be condemned. Only with surgical excision is there absolute certainty that the lesion has been completely eradicated, and only by this method is a specimen obtained for histopathologic study. A junction nevus or malignant melanoma may be excised by cautery, but the better cosmetic results and the preservation of a more suitable biopsy specimen make cold dissection preferable.

The treatment of malignant melanoma at present is purely surgical. If the tumor is removed before puberty or is one which developed in precancerous melanosis, local excision is usually sufficient. Radiation treatment has not proved to be adequate for either cure or palliation. The most important single factor in the surgical management of a patient with malignant melanoma is early operation, for which an early diagnosis is a prerequisite.

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